Florida Department of Health

Contaminated Steroid Product from New England Compounding Center (NECC) Guidance	Focus Area: Clinical
Guidance document number 2012-2	

Fungal Meningitis and Stroke Associated with Potentially Contaminated Steroid Product from NECC

Version 2.0 October 7, 2012

Note: This document may become outdated as situations change. Documents on this topic dated after October 7, 2012 supersede this one. This document will be posted on the Bureau of Epidemiology website http://www.doh.state.fl.us/Disease_ctrl/epi/index.html

Summary (10/7/12)

The Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) are coordinating a multi-state investigation of fungal meningitis among patients who received an epidural steroid injection. Several of these patients also suffered strokes that are believed to have resulted from their infection. As of October 7, 2012, 91 cases and seven deaths have been reported from nine states including Florida*. Four cases have been identified in Florida. Fungal meningitis is not transmitted from person to person. These cases are associated with a potentially contaminated medication. Investigation into the source is ongoing; however, all infected patients received at least one injection with preservative-free methylprednisolone acetate (80mg/ml) (MPA) prepared by New England Compounding Center, located in Framingham, Massachusetts.

All patients who have been exposed via epidural or other injection to the implicated product from NECC (lot numbers listed below), and present to a clinic in one of the affected communities or elsewhere in Florida should be evaluated for signs of meningitis or stroke so they can be tested and treated appropriately. **It is important to note that some, and perhaps most, patients will not have classic signs or symptoms of bacterial meningitis.** In particular severe headache, fever and meningismus may be minimal. **Please use a low threshold for lumbar puncture.** Testing and treatment guidance are included below.

Please immediately report all illnesses in patients injected with the implicated steroid products to your local county health department or the Florida Department of Health Bureau of Epidemiology at 850-245-4401. Although the product has been recalled and we currently believe that no patients in Florida are at further risk of exposure, due to the lengthy incubation period **we expect to detect new cases associated with this outbreak for several weeks.**

The product, from three implicated lots:

- Methylprednisolone Acetate (PF) 80 mg/ml Injection, Lot #05212012@68, by use date (BUD) 11/17/2012
- Methylprednisolone Acetate (PF) 80 mg/ml Injection, Lot #06292012@26, BUD 12/26/2012
- Methylprednisolone Acetate (PF) 80 mg/ml Injection, Lot #08102012@51, BUD 2/6/2013

was distributed to eight healthcare facilities in Florida:

Florida Pain Clinic, Ocala, FL	**Orlando Center for Outpatient Surgery,** Orlando, FL
Interventional Rehab Center, Pensacola, FL	**Pain Consultants of West Florida,** Pensacola, FL
Marion Pain Management Center, Ocala, FL	**Surgery Center of Ocala,** Ocala, FL
North County Surgicenter, Palm Beach, FL	**Surgical Park Center,** Miami, FL

Background

On September 21, 2012, CDC was notified by the Tennessee Department of Health of a patient with onset of meningitis approximately 19 days following epidural steroid injection at a Tennessee ambulatory surgery center (ASC). Initial cultures of cerebrospinal fluid (CSF) and blood were negative; subsequently, *Aspergillus fumigatus* was isolated from CSF by fungal culture. On September 28, investigators identified a case outside of Tennessee, possibly indicating contamination of a widely distributed medication. Several species of fungi have been identified in specimens obtained from subsequent patients.

Infected patients have presented approximately 1 to 4 weeks following their injection with a variety of symptoms, including fever, new or worsening headache, nausea, and new neurological deficit (consistent with deep brain stroke). Some of these patients had very mild symptoms. CSF has typically shown elevated white cell count (with a predominance of neutrophils), low glucose, and elevated protein.

Recall

On September 25, 2012, the New England Compounding Center (NECC) located in Framingham, MA voluntarily recalled the following lots of methylprednisolone acetate (PF) 80mg/ml:

1. Methylprednisolone Acetate (PF) 80 mg/ml Injection, Lot #05212012@68, by use date (BUD) 11/17/2012
2. Methylprednisolone Acetate (PF) 80 mg/ml Injection, Lot #06292012@26, BUD 12/26/2012
3. Methylprednisolone Acetate (PF) 80 mg/ml Injection, Lot #08102012@51, BUD 2/6/2013

Nationwide, the lots were distributed to 23 states and 75 facilities; with 8 facilities in Florida receiving product (see list above). On October 3, 2012, the NECC ceased all production and initiated recall of all methylprednisolone acetate and other drug products prepared for intrathecal administration. On October 6, NECC announced a recall of all products currently in circulation that were compounded at and distributed from its facility in Framingham, Massachusetts.

At this time, patients who have had an injection (e.g., spinal, joint) with any of the three lots of methylprednisolone acetate listed above are being contacted by the facility where they received treatment. Although all cases detected to date occurred after injections with products from these three lots, out of an abundance of caution, CDC and FDA recommend that healthcare professionals cease use of any product produced by the NECC until further information is available. The complete list of Florida facilities who have received any NECC product can be found at the Florida Department of Health Online Newsroom: http://newsroom.doh.state.fl.us/

Recommendations

For patients who received epidural injection with MPA from one of the three lots listed above and have symptoms of meningitis or basilar stroke, a diagnostic lumbar puncture (LP) should be performed, if not contraindicated. **Because presenting symptoms of some patients with**

meningitis have been mild and not classic for meningitis (e.g., new or worsening headache without fever or neck stiffness), physicians should have a low threshold for performing a LP. While CDC is aware of infections occurring only in patients who have received epidural MPA injections, patients who received other types of injection with MPA from those three lots will also be contacted to assess for signs of infection (e.g., swelling, increasing pain, redness, warmth at the injection site) and should be encouraged to seek evaluation (e.g., arthrocentesis) if such symptoms exist.

Case Definition as of October 6, 2012

- A person with meningitis[1] of sub-acute onset (1-4 weeks) following epidural injection after July 1, 2012.
- A person, who has not received a lumbar puncture, with basilar stroke 1-4 weeks following epidural injection after July 1, 2012[2].
- A person with evidence of spinal osteomyelitis or epidural abscess at the site of an epidural injection diagnosed 1-4 weeks after epidural injection after July 1, 2012.

[1]clinically diagnosed meningitis meaning 1 or more of the following symptoms: headache, fever, stiff neck, or photophobia **and** a CSF profile consistent with meningitis (elevated protein/low glucose/pleocytosis)
[2]*These people should have an LP unless contra indicated.*

See below for guidance on diagnostic testing that should be performed on patient specimens. These are also available at http://www.cdc.gov/hai/outbreaks/meningitis.html. Clinicians should report any suspected adverse events following use of these products to FDA's MedWatch program at 1-800-332-1088 or www.fda.gov/medwatch.

Instructions for Clinical Teams Regarding Diagnostic Testing – Outbreak of Unknown Meningitis

CDC, October 6, 2012

The pathogens involved in this cluster of infections are still under investigation. At present, there is culture or histopathologic evidence of fungal infection in at least nine patients; isolates have included *Aspergillus* spp. and *Exserohilum* spp. Because the pathogens associated with this outbreak may not have been fully determined, it is important to perform a thorough diagnostic work-up in exposed patient with signs and symptoms of CNS, parameningeal infections, or septic arthritis. The following CDC algorithm (with minor modification by FDOH) has been developed to help guide clinicians in their diagnostic work-up. These instructions are meant to supplement routine laboratory and microbiologic test deemed necessary by the clinical team and should not replace existing diagnostic protocol.

Cerebrospinal fluid (CSF):

- When possible collect a large volume of cerebrospinal fluid (CSF).
- Routine tests should include total cell count (WBC and RBC), differential cell count, glucose (CSF/plasma ratio), and total protein.
- Obtain routine Gram stain and bacterial cultures (including aerobic and anaerobic). The priority for remaining CSF specimens is fungal culture, conducted at the local hospital or state lab. When possible submit a large volume of CSF (minimum 10 mL) for fungal culture.
- Remaining CSF should be sent to CDC for PCR analysis; minimum amount should be 1 mL, but submit 5 mL if possible. Samples sent to CDC should be unspun samples or a freshly collected, unadulterated sample.[1]

- Specifically for the work-up of possible fungal pathogens:
    - If patients have intraventricular shunts or drains, obtain large volume of CSF to culture for fungi from this source.
    - Send CSF sample for *Aspergillus* galactomannan assay[2] if there is any remaining CSF available after fungal culture and sample for PCR have been sent to CDC.
- All cultures should be held for at least 2 weeks prior to discarding.

Serum:

- Send specimen for *Aspergillus* galactomannan assay.

Other tests:

- In addition to routine blood cultures, consider obtaining fungal and AFB blood cultures.
- Other potentially infected fluid collections should be sampled (e.g., aspiration of epidural abscess, synovial fluid) and sent for microbiologic testing as described above for CSF specimens (including fungal smear).

Tissue specimens (including post mortem specimens):

- Any relevant tissue specimens sent for histopathology should be stained and reviewed for infectious agents, including fungi (silver stain). Please save specimens to send to state health departments and CDC for further evaluation.
- Please send available autopsy specimens to CDC for further evaluation. Contact your County Health Department[1] for guidance for specimen collection and processing.

- Tissue specimens
    - Please use IDPB CNS submission guidelines and General Unexplained Illness Submission Guidelines posted on CDC website.

[1] Please contact your County Health Department or the Florida Department of Health, Bureau of Epidemiology (850-245-4401) to coordinate shipment of specimens to CDC for further testing.

[2] The Aspergillus galactomannan assay (Platelia; BioRad) has been FDA approved only for serum. However there are some published case series reporting its utility in identifying cases of Aspergillus meningitis, where the test has been done on CSF samples on a research basis.

Interim Treatment Options — Outbreak of Unknown Meningitis
CDC, October 3, 2012 (updated by FDOH)

Several species of fungi (*Aspergillus* and *Exserohilum*) have been isolated from CSF and histopathologic evidence of fungal infection has been found in several postmortem specimens from patients linked to the outbreak. The possibility that the product has also been contaminated with bacteria has not been excluded although there are no confirmed cases of bacterial meningitis reported to date. When treating patients with meningitis who likely meet the outbreak case definition, clinicians should continue to follow routine treatment protocols for meningitis of unclear etiology, including covering for potential bacterial causes of meningitis. In addition, until the etiology is better defined, clinicians are encouraged to add

empiric antifungal therapy to the treatment regimen because of the severe adverse outcomes of untreated fungal meningitis. CDC has consulted with national experts on the following guidance; these treatment options for fungal meningitis in patients associated with this cluster are interim, and may change as new information becomes available.

Initiate empiric antifungal therapy using the following regimen:

- At a minimum, all patients should receive voriconazole (if no contraindications), preferably at a dose of 6mg/kg every 12 hours (IV initially) and to continue on this high dose for the duration of treatment, if possible. Periodic monitoring of serum concentration is advisable.

- Consider combination therapy with liposomal Amphotericin B (preferred over other lipid formulations), preferably at a higher dose of 7.5 mg/kg IV daily. If nephrotoxicity is a potential concern, particularly in older patients, the dose may be decreased to 5mg/kg IV daily. Administration of 1L normal saline prior to infusion may be considered to minimize risk of nephrotoxicity.

- Avoid use of intrathecal amphotericin B, either the deoxycholate or the lipid formulations, due to limited data on its use and associated toxicities.

There is currently no clear evidence for the use of adjuvant steroid therapy. If used, careful monitoring of clinical status is warranted.

Adequate duration of treatment is unknown but likely will require prolonged antifungal therapy (e.g., months) tailored by the clinical response to infection. Individual management decisions, including choice of long-term antifungal regimen, should be made in consultation with infectious disease physicians experienced in the treatment of fungal meningitis. Clinicians should be vigilant for potential relapse of infection.